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ORIGINAL ARTICLE

Preparation and *in vitro* evaluation of rutin nanostructured liquisolid delivery system

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Abstract Poor aqueous solubility of chemical entities presents a major challenge to modern drug delivery, because of their low bioavailability. Our aim was to prepare and evaluate a suitable solid self-emulsifying drug delivery system (SSEDDS) as a potential carrier for rutin. After screening of various vehicles (surfactants, co-surfactants and oils) and selection of those having the better drug solubilizing power, liquid SEDDS were formulated. Prepared formulations were evaluated for self-emulsifying ability and phase diagrams were constructed to optimize the systems. System (S6), prepared from Triton/Acconon/Labrafac, attained highest drug solubilization capacity, hence, was selected for the preparation of SSEDDS by adsorption on different nano-structured carriers (Neusilin®, Fujicalin® and F-melt®) in different ratios. S6 had a very small particle size of 4.849 ± 0.001 nm and a high percentage transmittance of 99.31 ± 0.16%. SSEDDS showing good flow properties as well as reasonable drug loading capacity were selected for *in vitro* drug release studies. The SSEDDS (SS4) composed of Neusilin® US2: S6 (1:2) attained the best drug release properties and was subjected to further characterization (SEM, FTIR and XRD). Conclusion: The optimized liquisolid dosage form of rutin provided good flowability as well as fast drug release properties and, therefore, can be suitable for oral delivery system.

1. Introduction

Many drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Hence, oral delivery of numerous drugs, including rutin, is hindered owing to their high hydrophobicity.[1,2] Therefore, producing suitable formulations are essential to improve the solubility and bioavailability of such drugs. Rutin is a polyphenolic compound having diverse pharmacological activities including antiallergic, anti-inflammatory,[3] vasoactive, antitumor, antibacterial, antiviral and anti-protozoal properties,[4] hypolipidaemic, cytoprotective, antispasmodic and anticarcinogenic effects.[5] Its poor solubility in aqueous media is the reason for its poor bioavailability. Oral administration is desired for the administration of rutin as nutritional supplement in a dose of 60 mg to be taken three times daily.[2,6]

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One of the most popular and commercially viable formulation approaches for solving the problems of low oral bioavailability is self-emulsifying drug delivery systems (SEDDS). SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble drugs.[7] SEDDS, which belong to lipid-based formulations, are isotropic mixtures of drug, oil/lipid, surfactant, and/or co-surfactant, which form fine emulsion/lipid droplets, ranging in size from approximately 100 nm to <50 nm, on dilution with physiological fluid. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state.[8] Presence of the surfactant in the microemulsion structure, being dispersed in the gastric content, will allow a portion of the added surfactants to be located at the O/W interface. Therefore, the concentration of the free surfactant in the emulsion water phase is probably much lower than its nominal concentration in the entire emulsion, thus decreasing the toxic effect attributed to the free surfactant.[9]

Traditional preparation of SEDDS is normally present as liquids, the preparation technique involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, this technique has some disadvantages, for example, low stability, difficult portability, and few choices of dosage forms. Irreversible drugs/excipients precipitation may also be problematic.[10] More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation. To address these problems, solid SEDDS (SSEDDS) have been investigated, as alternative approaches. Such systems require the solidification of liquid self-emulsifying (SE) ingredients into powders/nanoparticles to create various solid dosage forms.[11] Thus, SSEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, and better patient compliance).

Free flowing powders may be obtained from liquid SEDDS by adsorption onto solid carriers. A significant benefit of the adsorption technique is the good content uniformity.[12] Liquisolid systems are composed of a non-volatile, water miscible liquid vehicle, solid drug particles, and selected excipients, namely the carrier. The liquid portion, which can be a liquid drug, a drug suspension, or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Thus, an apparently dry, free flowing, and compressible powder is obtained.[13]Stability studies with liquisolid systems containing various drugs[14] showed that storage at different conditions neither had an effect on their flow nor release properties. This indicates that the technology is a promising technique for release enhancement, which is not associated with any physical stability issues. Besides drug release enhancement, the liquisolid approach is a promising technique because of the simple manufacturing process as well as low production costs.[13]

However, it is very important to search for more efficient excipients which have higher adsorption capacities and faster drug release to improve liquisolid formulations. Fortunately, it is interesting that there are some recent pharmaceutical excipients which have nano-structures[15] like F-melt®, Fujicalin® and Neusilin® US2.[16,17] These are low density, porous carriers with a high surface area.

Some previous studies were aiming to improve rutin bioavailability[2,6,18]; however, this is the first study focusing on this type of delivery systems.

The aim of this study was to investigate SEDDS as a potential drug delivery system for the poorly water soluble drug rutin. Several oils, surfactants (S) and co-surfactants (CoS) were screened for their rutin solubilizing power. Different blends of the best solubilizing S, CoS and oils were done to obtain an optimized SEDDS. The selected SEDDS were characterized and adsorbed on three different nano-structured carriers (F-melt®, Fujicalin® and Neusilin®), then the influence of these solid carriers on drug dissolution and SSEDDS flow properties was investigated.

2. Materials and Methods

2.1. Materials

Rutin was a kind gift from Kahira Pharmaceutical and Ind. Co., Cairo, Egypt. Labrasol® (PEG-6 caprylic/capric triglycerides), Plurol® Oleique CC 497 (polyglyceryl-3 dioleate), Labrafac® PG (propylene glycol dicaprylocaprate), Capryol™ 90 (propylene glycol monocaprylate) and Labrafil® M 1944 LS (decyl polyglucoside) were gift samples from Gattefossé, France. Simulosol® 1292DF was supplied from SEPPIC, France. Capmul® MCM C8 (glyceryl monocaprylate), Acconon® MC8-2 EP/NF (polyoxyethylene (8) caprylic/capric glycerides) and Captex® 200 (propylene glycol dicaprylocaprate) were obtained as gift samples from ABITEC Corporations, Cleveland, USA. Miranol® C2 M was provided by Rhodia Inc, USA. Poly ethylene glycol 400, propylene glycol, Diacetin®, methyl laurate, isopropyl myristate, isopropyl palmitate, oleic acid, Triton® X-100 (polyoxyethylene (10) octylphenyl ether) and ethanol were purchased from Sigma Chemical Company, St. Louis, USA. Miglyol® 812 (caprylic/capric triglyceride) was kindly provided by Sasol Germany GmbH, Witten, Germany. Neusilin® US2, F-melt® type M and Fujiculin® were gifted from Fuji Chemical Industry CO., Ltd. (Toyama, Japan). All other chemicals used were of analytical grade.

2.2. Screening study

To select the oils, surfactants (S) and co-surfactants (coS) having the highest solubilizing capacity of the drug, screening of the different components was carried out. As a preliminary experiment, drug solubility was determined qualitatively by visual observation of solution transparency and presence of any drug crystals.[19,20] Briefly, 10 mg of drug and increasing quantities of the tested components in 10 ml glass vials were shaken at 100 rpm in a controlled temperature water bath at 37 ± 1 °C (Memmert Gmgh, Germany) to facilitate the solubilization. The solubility of the drug was observed visually and the amount needed to give a clear solution when seen with the naked eye under normal light was recorded.

2.3. Preparation of SEDDS

A series of SEDDS formulations were prepared using the components selected from the screening study with the surfactant: co-surfactant to oil (S/CoS/oil) ratio was equal to 80:10:10.

Briefly, rutin (10 mg) was dissolved in surfactant phase (S/Co S) followed by the addition of oil in screw capped glass vials. The produced blends were then stirred continuously by vortex mixing (JULABO Labortechnik, Germany) and left to equilibrate for 24 h at ambient temperature to obtain a homogenous isotropic mixture. The SEDDS formulations were stored at ambient temperature until further use.

2.4. Assessment of self-emulsification

The first step toward the formulation of SEDDS is to determine the feasibility of being self-emulsified upon dilution. In order to evaluate the self emulsifying properties of the SEDDS formulations, one gram of each formulation was added dropwise into a beaker containing 20 ml of distilled water maintained at 37 ± 0.5 °C stirred using a magnetic stirrer at 100 rpm. The process of self-emulsification was assessed visually as reported and the appearance of the produced emulsions was evaluated using the following grading.[21,22]

A: Denoting the rapid formation of a clear nanoemulsion (within 1 min.).
B: Denoting the formation of a translucent nanoemulsion.
C: Represent the formation of a less clear emulsion which had a bluish white appearance.
D: Denoting the formation of a bright white emulsion (similar in appearance to milk).
E: Denoting the formulations which exhibited either poor emulsification with large oil droplets on the surface or the emulsion was not formed.

2.5. Construction of ternary phase diagram

Phase diagrams identifying the self emulsifying region were constructed for Type A emulsions. Ternary diagrams of surfactants, co-surfactants, and oil were plotted; each of them representing an apex of the triangle. Ternary mixtures with varying compositions of surfactant, co-surfactant, and oil were prepared. Various combinations of surfactant, co-surfactant, and oil were prepared. The prepared systems were visually analyzed for any phase separation under storage for 72 h at ambient temperature. The compositions were evaluated for nanoemulsion formation by diluting one part of pre-concentrate with deionized water (1:20). The nanoemulsion regions in the diagrams were plotted, and the wider region indicated better self-nanoemulsification efficiency.[23]

Based on the obtained diagrams, appropriate concentrations of surfactant, co-surfactant and oil were selected for further investigation.

2.6. Assessment of rutin solubility in the selected systems

An excess amount of rutin was added to the screw-capped test tubes containing 4 ml of the selected systems and then stirred for 5 min by a vortex mixer. The mixtures were then shaken in an isothermal water bath shaker at 37 ± 1 °C for 72 h (Memmert Gmgh, Germany). After reaching equilibrium, each tube was centrifuged at 9000 rpm for 60 min, filtered through a 0.2 μm Millipore membrane filter, appropriately diluted with methanol and then the amount of rutin was determined spectrophotometrically at 357.5 nm (Shimadzu UV spectrophotometer, 2401/PC, Japan).

2.7. Characterization of rutin SEDDS

Depending on rutin solubility in the prepared systems, the formulation with the highest drug solubilization capacity was selected for characterization and further investigation. Rutin-loaded SEDDS formulation was prepared by dissolving rutin (maximum amount entrapped based on a previous solubility study) in the formed SEDDS (20 g) by stirring at 40 °C till a clear, transparent system was produced which was then stored at ambient temperature for 48 h before investigations.

2.8. Droplet size determination

The average droplet size and its distribution of the produced rutin-loaded SEDDS were measured using a Zetasizer Nano-ZS (Malvern Instruments, UK). SEDDS was diluted with a ratio of 1:10 (v/v) with distilled water. The measurement was done at 25 °C.

2.9. Percentage transmittance (λ_{max}, 560 nm)

A total of 1 mL of SEDDS formulation was diluted 100 times with deionized water. Percentage transmittance was measured spectrophotometrically (Shimadzu UV spectrophotometer, 2401/PC, Japan) at 560 nm using deionized water as a blank.[23]

2.10. Preparation of rutin liquisolid powders

Liquisolid powders or solid SEDDS (SSEDDS) were produced by adding rutin loaded SEDDS formulation dropwise to the following adsorbents: Neusilin® US2, F-melt® type M and Fujiculin®, where SEDDS/adsorbent weight ratio varied between 1:3, 1:2, 1:1, 2:1 and 3:1. The blends were then mixed and grinded for 15 min using a mortar and pestle until homogenous mixtures were formed. The obtained powders were left for 24 h at ambient temperature before further characterization.

2.11. Evaluation of liquisolid powders flow properties

The flow properties of the produced liquisolid systems were evaluated by measuring the following parameters: angle of repose, Carr's index and Hausner's ratio. The angle of repose (θ) was measured according to the conventional fixed height cone method.[24] The powder was poured through a funnel with its tip positioned at a fixed height (H) until the apex of the conical pile formed just reaches the tip of the funnel. The angle of repose was calculated using the formula $\tan\theta = H/r$ where r is radius of the pile of powder.

The Carr's (compressibility) index and Hausner's ratio were calculated from the bulk and tapped density of the tested powder.[24] The powder was poured lightly into a 25 ml graduated cylinder. The powder was tapped until no further change in volume was observed. Powder bulk density, ρ_b (g/cm^3), and powder tapped density, ρ_p (g/cm^3) were calculated as the weight of the powder divided by its volume before and after tapping, respectively. Percentage compressibility was computed from the following equation:

Carrs Index $= \rho_p - \rho_b/\rho_p \times 100$

The Hausner's ratio is calculated according to the following equation: Hausner's Ratio = volume before tapping/volume after tapping. All tests were performed in triplicate and the average was calculated for each powder.

2.12. In-vitro drug release studies

SSEDDS powders showing acceptable flow properties were studied for their *in vitro* drug release properties using USP Apparatus I, using a 0.5 μ mesh[25] (rotating basket) (Hanson SR8plus, USA). One gram of the tested powder was transferred to a 400 ml receptor medium which consisted of phosphate buffer pH 6.8[23,26–28] containing 15% methyl alcohol to maintain sink condition at a speed of 100 rpm and the temperature was maintained at 37 ± 0.5 °C. At predetermined time intervals (10, 20, 30, 45, 60, 90, 120 and 180 min), aliquots of 5 ml were withdrawn and replaced by fresh solution in order to maintain sink condition throughout the experiment. The withdrawn samples were filtered through a 0.2 μm Millipore membrane and then analyzed for drug content spectrophotometrically at 367 nm. Release profiles were plotted and release efficiency was calculated.[29] The experiments were carried out in triplicate and data were expressed as mean value ± S.D.

2.13. Characterization of selected liquisolid powder

2.13.1. Particle size and size distribution

The mean particle size and particle size distribution of the selected liquisolid powder were performed by photon correlation spectroscopy (Malvern Instrument Ltd., Worcestershire, United Kingdom). Before measurement, the sample was appropriately diluted with double distilled water measured at 25 °C with an angle of detection of 90°.

2.13.2. Scanning electron microscopy (SEM)

The surface characteristics of the selected liquisolid powder were investigated by scanning electron microscope (SEM) (JXA-840 A, JEOL, Tokyo, Japan). The sample was placed on a clear glass stub and sputter-coated with a thin layer of gold using a vacuum evaporator. SEM images were examined using a SEM equipped with a digital camera, at 20 kV accelerating voltage.

2.13.3. X-ray powder diffractometry (XRPD)

X-ray powder diffraction patterns of rutin, adsorbent and selected liquisolid powder were recorded on a Diano X-ray diffractometer (Scintag Inc., USA). Samples were irradiated using Ni filtered, CuKα radiation at a voltage of 45 kV, and a 9 mA current. The scanning rate employed was 1° min^{-1} over 0° to 90° diffraction angle (2θ) range.

2.13.4. Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra of rutin, adsorbent and selected liquisolid powder were obtained using FT-IR spectrophotometer (Shimadzu 435 U-O4 IR spectrophotometer, Japan). Rutin, adsorbent and selected liquisolid powder were mixed separately with IR grade KBr in the ratio of 100:1 and the corresponding disks were prepared by applying a 5.5 metric ton of pressure in a hydraulic press. The disks were scanned over a wave number range 4000–400 cm^{-1}.

2.14. Data analysis

All experiments were performed three times and the data were expressed as mean ± standard deviation (S.D.). The statistical significance of differences was determined by ANOVA using SPSS® software (Version 17, Chicago). A value of $p < 0.05$ was considered to be significant.

3. Results and discussion

3.1. Screening study

Drug loading per formulation is a critical design factor which can be dependent on its solubility in various formulation components.[21] Drug may be solubilized in the oily core and/or on the interface of these structures, so the selected vehicles should have a good solubilizing power to the drug.[30] Therefore, the solubility of rutin in individual system components (oil, surfactant, and co-surfactant) was tested for proper component selection for ternary phase diagram study, and the results are presented in Table 1. As a preformulation step, drug solubility in different components was determined visually till no drug crystals were detected indicating that it was dissolved.[20] Starting with the oily phase, both long and medium chain triglyceride oils with different degrees of saturation were screened. Based on the obtained data, oleic acid (OA) as well as Labrafac (Labc) showed the highest drug solubilizing effect (least amount needed to dissolve the drug) and therefore were chosen for ternary phase diagram study. The best solubilizing effect of oleic acid was previously reported.[31,32] Labc is a medium chain fatty acid ester having a low HLB value (2) and can be used as an oily vehicle in oral formulations especially self emulsifying formulations, it's good solubilizing effect for lipophilic drugs was previously afforded.[33,34] The selected oils for further investigations (OA and Labc) have fair fluidity, proper self-emulsification properties and are efficiently digested.[35] All other tested oils showed poor rutin solubilizing power.

Concerning surfactants, Diacetin® (glycerol diacetate) which is known to be a good solvent,[36] showed an excellent rutin solubilizing effect. Similarly, Labrasol® (Labl) having an HLB value of 14 and composed of polyoxyethylene groups which can interact with rutin showed high solubilization capacity, similar high solubilizing properties of Labl were previously found for curcumin.[34] Also, Triton® X-100 (TX) which is polyoxyethylene (POE) surfactant attained high drug solubilization. The good wetting properties of TX for a hydrophobic drug were previously recorded[37] and were attributed to the structurally "linear" and short POE chains. Previous studies involving the solubilizing effect of TX include the solubilization of clofazimine analogs,[38] carbamazepine[39] and bromhexine hydrochloride[40] by TX.

Regarding co-surfactants, ethanol (Eth), propylene glycol (PG) and Acconon® (AC) attained best drug solubilizing properties. According to earlier reports,[41] the co-surfactant can lower the interfacial tension of the surfactant in microemulsions, resulting in a more flexible and dynamic layer. The drug in this energy-rich system can diffuse across the flexible interfacial surfactant film between the phases; a

Table 1 Screening of various components for rutin solubility.

Component	Amount needed to solubilize 10 mg rutin (gm)
Oil	
Oleic acid	6.75 ± 0.354
Labrafac PG	7.50 ± 0.000
Isopropyl myristate	11.25 ± 1.768
Isopropyl palmitate	11.00 ± 1.414
Methyl Laurate	> 10
Miglyol 812	> 10
Miranol	> 10
Surfactant	
Diacetin	1.25 ± 0.354
Labrasol	2.75 ± 0.354
Capmul MCM C8	7.75 ± 1.061
Triton X-100	6.5 ± 0.707
Captex 200	> 10
Plurol Oleique CC 497	> 10
Labrafil M 1944 LS	> 10
Simulosol 1292DF	> 10
Co-surfactant	
Ethanol	0.50 ± 0.000
PG	1.25 ± 0.354
PEG 400	2.50 ± 0.707
Acconon MC8	2.00 ± 0.000
Capryol™ 90	> 10

thermodynamic process that increases partitioning and diffusion. It can decrease the fluidity of SEDDS, enhances drug incorporation into the SEDDS, improves self-emulsification properties, and possesses penetration enhancement effect.[42] Also, it can reduce the required amount of surfactant.[32]

Therefore, different combinations of the following components, OA and Labc (oils), Diacetin, Labl and TX (surfactants) and Eth, PG and AC (co-surfactants) have been tested for their potential to formulate successful self-emulsifying systems (SEDDS) consisting of (S/CoS/oil) in a 80/10/10 ratio as a preliminary study.

3.2. Assessment of self-emulsification

SEDDS were prepared and their self-emulsifying properties were visually observed, these systems should be a clear, monophasic liquid when introduced into aqueous medium and should have good solubilizing properties to present the drug in a solution. Also, individual components should have good miscibility with each other to produce a stable formulation.[26]

The visual grading of the process of self-emulsification upon dilution as well as the composition of tested SEDDS is shown in Table 2. It is obvious that only S1, S2, S3, S6 and S7 presented type A and were selected for further investigation, namely, construction of ternary-phase diagram.

We can say that the S/CoS/oil combinations used to formulate the systems listed above increased the spontaneity of the self-emulsification process and the efficiency of emulsification was good, allowing spontaneous fine emulsion formation. It is well known that low particle size can allow the formation of a more clear-appearing emulsion.[43]

3.3. Construction of ternary phase diagram

The existence of self-emulsifying oil formulation fields that could self-emulsify under dilution and gentle agitation was identified from ternary phase diagrams (Fig. 1) of systems containing S/CoS/oil, the outer parallelogram indicates the location of microemulsification region. This can allow the optimization of the oil, surfactant and co-surfactant concentrations used. In all cases, only compositions containing $\leqslant$10% oil were capable of self-emulsification. This could be explained by the fact that the surfactant stabilizes the O/W interface and its concentration increased at the interface upon decreasing the oily content. Also, it is known that increasing oil concentration increases particle size[43] which opposes clear emulsion formation.

It can be also observed that increasing S/CoS ratio increased the probability of formation of successful SEDDS this runs in parallel with some literature.[44] The droplet size of the emulsion is a crucial factor in self-emulsification performance. It was previously reported that increasing the surfactant concentration in the SEDDS formula decreased the particle diameter of the emulsion formed which increases the probability of SEDDS formation.[45] The higher the proportion of surfactant in the system, the greater is the spontaneity of emulsification, this may be due to excess penetration of aqueous phase into the oil phase causing massive interfacial disruption and ejection of droplets into the bulk aqueous phase.[42] Also, previous reports indicated that the amount of CoS was inversely proportional to emulsion stability.[46]

S2 composed of TX/Eth/OA showed the wider microemulsion area and isotropic regions and was capable of the formation of SEDDS with the S/CoS/oil ratio reaching 5/4/1. This

Table 2 Visual assessment of efficiency of self-microemulsification and solubility of rutin in selected SEDDS (type A) at 37 °C.

System	Composition (S/CoS/oil: 80/10/10)	Visual grade	Rutin solubility (mg/ml)
S1	Triton/PG/OA	A	0.380 ± 0.006
S2	Triton/Ethanol/OA	A	0.295 ± 0.002
S3	Triton/AC/OA	A	0.287 ± 0.036
S4	Triton/PG/Labrafac	C	–
S5	Triton/Ethanol/Labrafac	C	–
S6	Triton/Acconon/Labrafac	A	1.444 ± 0.238
S7	Labrasol/Acconon/OA	A	0.920 ± 0.0452
S8	Labrasol/Acconon/Labrafac	D	–
S9	Diacetin/Acconon/OA	E	–
S10	Diacetin/PG/OA	E	–
S11	Diacetin/Ethanol/OA	E	–
S12	Diacetin/Acconon/Labrafac	E	–
S13	Diacetin/PG/Labrafac	E	–
S14	Diacetin/Ethanol/Labrafac	E	–

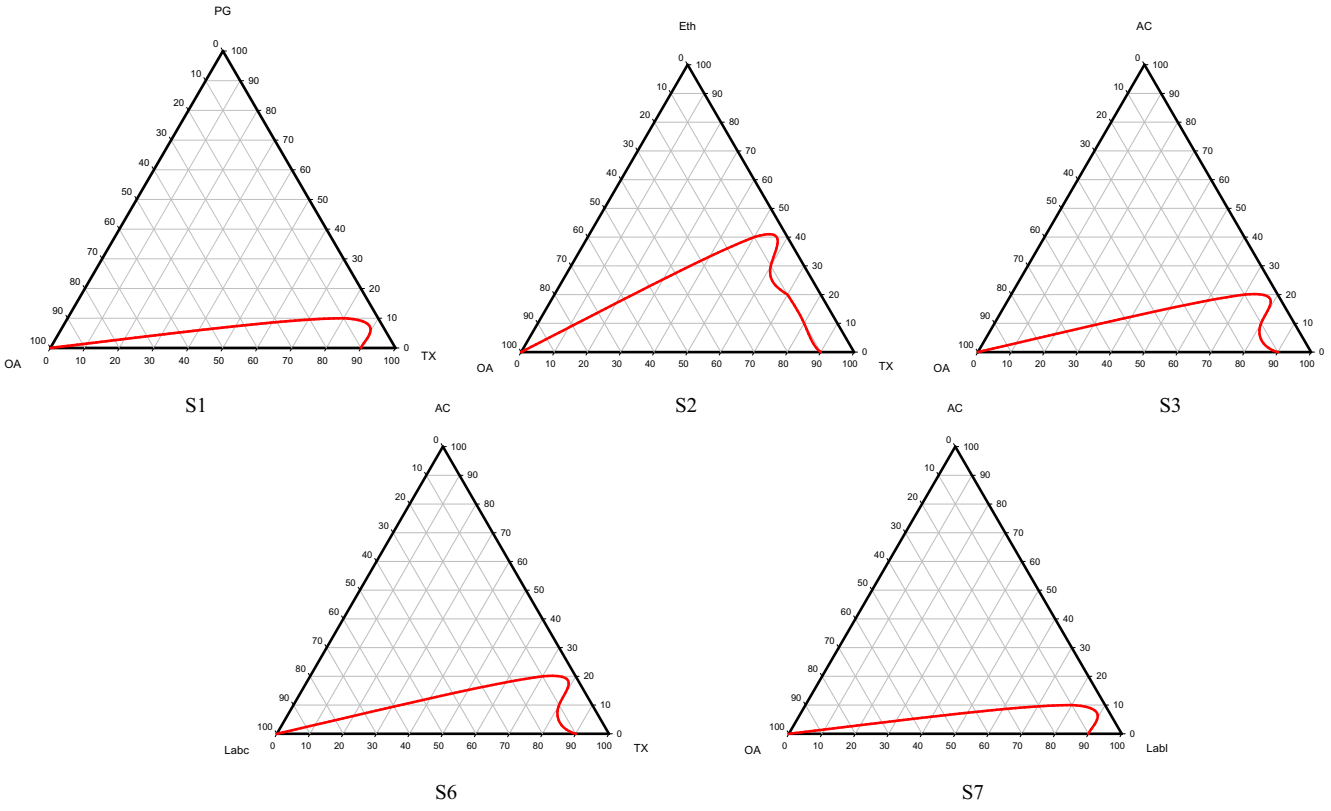

Figure 1 Ternary phase diagram of selected SEDDS (red boundries are indicating nanoemulsion regions).

can be attributed to the presence of ethanol; a previous work about microemulsion systems had shown that an ethanol co-surfactant was necessary to maintain a stable single phase O/W emulsion.[47] Our results run in parallel with a previous study showing that systems containing ethanol as CoS attained a maximum area of microemulsion zone.[48]

3.4. Assessment of rutin solubility in the selected systems

Drug loading is a key factor for the selection of the suitable formulation, a good balance between drug loading and efficient emulsification is required. To judiciously compare between different type A systems, the common S/CoS/oil ratio forming SEDDS in all cases which is 80/10/10, was applied to formulate systems in order to investigate rutin solubility. From Table 2, we can observe that S6, prepared from TX/AC/Labc attained highest drug solubilization capacity ($p < 0.05$). A proper justification can be the good wetting properties of TXP BS[37] and the structurally "linear" and short POE chains which can allow for a strong interaction with the great number of free hydroxyl groups bared by the polyphenolic drug. The best solubilizing power of TX was previously reported.[38–40]

TX is a nonionic surfactant with a high HLB value (17.6) while, AC is a nonionic emulsifier with a high HLB value

too (14). Co-surfactants should be chosen for their poor affinity either with the continuous or the dispersed phase. The proper co-surfactant will migrate to the oil/water interface and form a mixed S/CoS film. The CoS causes a transitory lowering of the interfacial tension during the formation of the dispersion.[49] It is well known that a surfactant mixture with higher HLB value is better for the formation of oil in water nanoemulsions.[50]

The good solubility of the drug in the surfactant, CoS and oil together with the proper S/CoS/oil combinations and the high surfactant HLB value may be other causes of the highest drug loading in S6. Therefore, this was the selected SEDDS for characterization and for preparation of the solid SEDDS (SSEDDS).

3.5. Characterization of selected SEDDS

The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as absorption. As shown in Fig. 2, S6 possessed a small droplet size of 4.849 ± 0.001 nm with a polydispersity index (PDI) of 0.14 ± 0.003 showing monomodal droplet size distribution. This small droplet size might be attributed to the higher S/CoS ratio as it was previously reported that increasing the surfactant concentration in the SEDDS formula decreased the particle diameter of the emulsion formed which increases the probability of SEDDS formation.[45] A small droplet size indicates a stable formulation and rapid emulsification.[51]

Similarly, a previous study has shown that the system containing Labc, with a relatively short chain fatty acid, attained a small droplet size.[52] It is well known that the chain length of the oil plays a role in the ease of emulsification, stabilization of the emulsions, as well as the emulsion droplet size.

Percentage transmittance of S6 after dilution for 100 times with deionized water was 99.31 ± 0.16%, such transmittance value having proximity to 100% indicates that clear nanoemulsion was formed when SEDDS was diluted with deionized water.

It was previously reported that, upon dilution, the two phases of a conventional emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the system. While, in the case of self-emulsifying systems, if the free energy required to form the emulsion is very low, then, the emulsification process occurs spontaneously.[53]

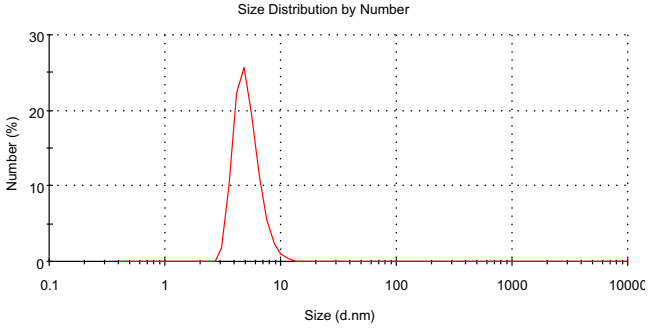

Figure 2 Droplet size and size distribution of S6.

3.6. Preparation and evaluation of liquisolid powders flow properties

Self-emulsifying powder was prepared to overcome the disadvantages associated with liquid SEDDS. Hence, to increase the stability and patient compliance the selected formulation, S6, was adsorbed onto different adsorbents at various carrier loads. However, specific carriers are required to allow obtaining the powder having superior flowability properties. The classification of flow properties based on "angle of repose", "Carr's index" and "Hausner ratio" is listed in Table 3.[54,55] S6 was adsorbed to several new carriers, namely, Neusilin®, Fujicalin® and F-melt® type M, these have a nano-structure allowing for high adsorption properties.As shown in Table 4, eleven SSEDDS were produced where the SEDDS: carrier ratio was varied from 3:1 to 1:3 or until reaching a cohesive powder mass which cannot be evaluated for its flow properties. The carrier as well as ratio variation was aiming to attain a free flowing powder having a high drug loading capacity. The latter was quantified using the following equation[56]:

$$Lf = W/Q$$

where, Lf is the liquid loading factor; W is the liquid medication (SEDDS) weight; Q is the carrier material weight.

F-MELT® is a co-spray dried excipient. It could be a proper strategy to improve the quality, performance and provide taste masking of solid oral dosage forms.[16,57]

Fujicalin® is a spray-dried second generation dibasic calcium phosphate anhydrous (DCPA) offering a new grade of DCPA with unique properties. With a typical voided cardhouse structure, Fujicalin® has significantly higher specific surface area and higher oil adsorption capacity than conventional DCPA. Fujicalin® particle's structure has high porosity; it retains 2 to 3 times higher porosity than other popular excipients. With its spherical shape and smooth surface, Fujicalin® is highly flowable and has excellent blending capacity which increases drug content uniformity of obtained formulations and reduces variation.

Neusilin® is a spray-dried totally synthetic, amorphous form of magnesium aluminometasilicate (MAS) that can be used both in pharmaceutical and cosmetic preparations. It has also been demonstrated as an excellent adsorbent carrier for solid dispersion and SEDDS[58] by simple mixing of

Table 3 Classification of flow properties.[54,55]

Angle of repose (θ)	Hausner ratio (HR)	Carr's index (CI)	Flow properties
< 30	< 1.25	< 15	excellent
30–40	1.25–1.50	15–25	good
> 40	> 1.50	> 25	poor

Table 4 SSEDDS flow properties.

Formula	Carrier	Carrier: SEDDS ratio	θ	HR	CI	Lf**
Rutin	–	–	–	–	–	–
SS 1		3:1	18.43 ± 0.22	1.14 ± 0.01	12.50 ± 0.64	0.33
SS 2	Neusilin® US2	2:1	20.12 ± 0.25	1.18 ± 0.01	17.94 ± 0.86	0.50
SS 3	Properties*	1:1	20.45 ± 0.24	1.20 ± 0.02	18.55 ± 0.54	1.00
SS 4	a = 300	1:2	24.33 ± 0.30	1.31 ± 0.01	22.92 ± 0.29	2.00
SS 5	b = 2.7–3.4	1:3	29.65 ± 0.21	1.34 ± 0.02	24.30 ± 0.51	3.00
	c =2.4–3.1					
SS 6	Fujicalin®	3:1	24.86 ± 0.19	1.23 ± 0.01	24.92 ± 0.34	0.33
SS 7	Properties*	2:1	26.56 ± 0.21	1.33 ± 0.02	25.08 ± 0.44	0.50
SS 8	a = 40	1:1	37.35 ± 0.26	1.51 ± 0.02	33.07 ± 0.39	1.00
SS 9	b = 1.1	1:2	–	–	–	2.00
	c = 1.2					
SS 10	F-melt (M)	3:1	44.30 ± 0.22	1.81 ± 0.03	42.60 ± 0.70	0.33
SS 11		2:1	–	–	–	0.50

* *a*: Specific surface area (m^2/g),[16,17] *b*: Oil adsorption capacity (ml/g), *c*: Water adsorption capacity (ml/g).
** Lf: loading factor.

crystalline drug and Neusilin®. Fuji's Neusilin® comes with high specific area, increased surface adsorption, porosity, anti-caking and flow enhancing properties.[17] These features of Neusilin® allow formulators to explore liquisolid technology to improve bioavailability and overcome problems associated with processing and stability of poorly water soluble drugs.[59] The physical and chemical stability of the amorphous state of drug-Neusilin® complexes is well documented.

Table 4 shows the flow properties and Lf of all formulated SSEDDS, it is obvious that SS9, SS11 as well as the drug powder itself were too cohesive to pass through the evaluation process. It can be detected that Neusilin® seems to be the best carrier allowing for the highest Lf (Lf for SS5 = 3) as well as good flow properties. On the other side, F-melt® did not show satisfactory results, as the formulated powder had poor flowability although having low drug loading capacity (Lf = 0.33). Fujicalin® showed intermediate results with SS8 having an Lf equal to 1 but showing slightly poor flowability, while SS9 (Lf = 0.5) had good flowability.

The previous results could be expected and are due to some differences in physical properties of the three tested carriers. F-melt has poor adsorption capacity, hence, is not suitable for liquisolid preparation, while both Fujicalin® and Neusilin® seem to have physical properties[16] (Table 4) encouraging their use for it.

Powders having poor flow properties, namely SS8 and SS10 (according to Table 3) were excluded from further investigation concerning the release of drug from formulated liquisolid powders. In addition, flowable powders allowing for higher Lf values were preferred. Although SS6 has slightly better flow properties when compared to SS5 ($p > 0.05$), its Lf value was too low. Therefore; only SS3, SS4, SS5 and SS7 were subjected to release study.

3.7. In-vitro drug release studies

The aim of our study was to improve rutin dissolution as well as flow properties. It is well known that SEDDS improve the oral bioavailability of poorly soluble drugs by improving the solubility and maintaining the drug in small droplets of oil, all over the gastrointestinal tract.[42] As well, liquisolid powder of poorly soluble drugs provides enhanced drug release due to its ability to adsorb the drug on its high surface area and thus improves drug wettability.[60] Accordingly, this optimized drug release allows improved drug absorption and thus higher oral bioavailability.[61]

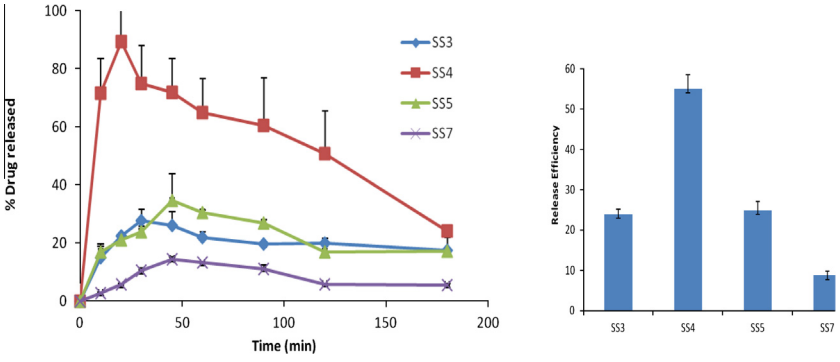

Figure 3 *In vitro* release profiles of rutin from SEDDS (Mean ± SD).

It is obvious from Fig. 3 that all SSEDDS containing Neusilin® (SS3, SS4 and SS5) showed far better release from that of Fujicalin® (SS7) ($p < 0.05$), this may be due to the difference in physical properties between both, favoring the better release properties of Neusilin®. The latter has a higher specific surface area and water adsorption capacity compared with the former (Table 4) which allows a facilitated wetting of drug-loaded particles and improved drug release from the SSEDDS.

Regarding the Neusilin® group, SS4 had the best drug release properties which can be seen in the release profiles and attained the highest release efficiency value ($p < 0.05$) (Fig. 2). This can be explained by the higher drug loading (Lf) compared to SS3, which increases drug concentration in the preparation and consequently increases the concentration gradient. The latter is an important release driving force. Further increase in drug loading (SS5) was not accompanied by improved release; this may be due to highly decreased flow properties (Table 4) and thus, particles aggregation. On the other hand, the higher Carr's index ($p < 0.05$) of SS4 compared to SS3 may be an indication of higher porosity of the former.[54,55] Increased porosity can allow rapid ingress of the dissolution medium inside the particles and facilitate drug diffusion out, resulting in a faster drug release.

3.8. Characterization of selected liquisolid powder

3.8.1. Particle size, size distribution and scanning electron microscopy (SEM)

Particle size analysis of the selected SSEDDS (SS4) demonstrated a monodisperse system with a mean diameter of 255.00 ± 0.001 nm having a polydispersity index (PDI) of 0.10 ± 0.001 indicating homogenous distribution.

Fig. 4 shows the scanning electron micrographs of SS4. The micrographs revealed that the solid SEDDS powder appeared as well separated almost spherical particles having nearly the same particle size obtained by size analysis. No separated

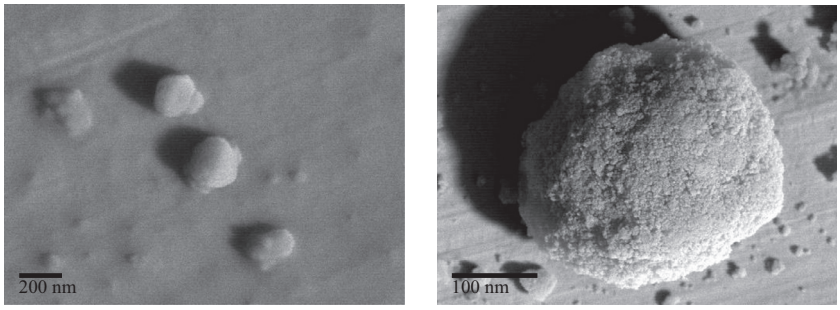

Figure 4 Scanning electron micrographs of SS4.

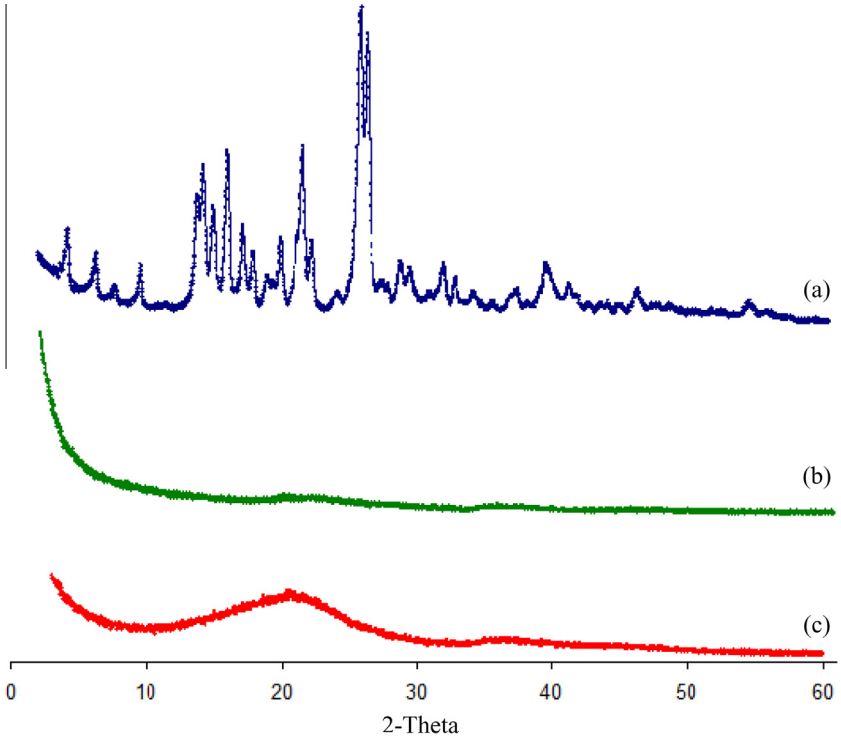

Figure 5 X-ray patterns of (a) rutin, (b) Neusilin and (c) SS4.

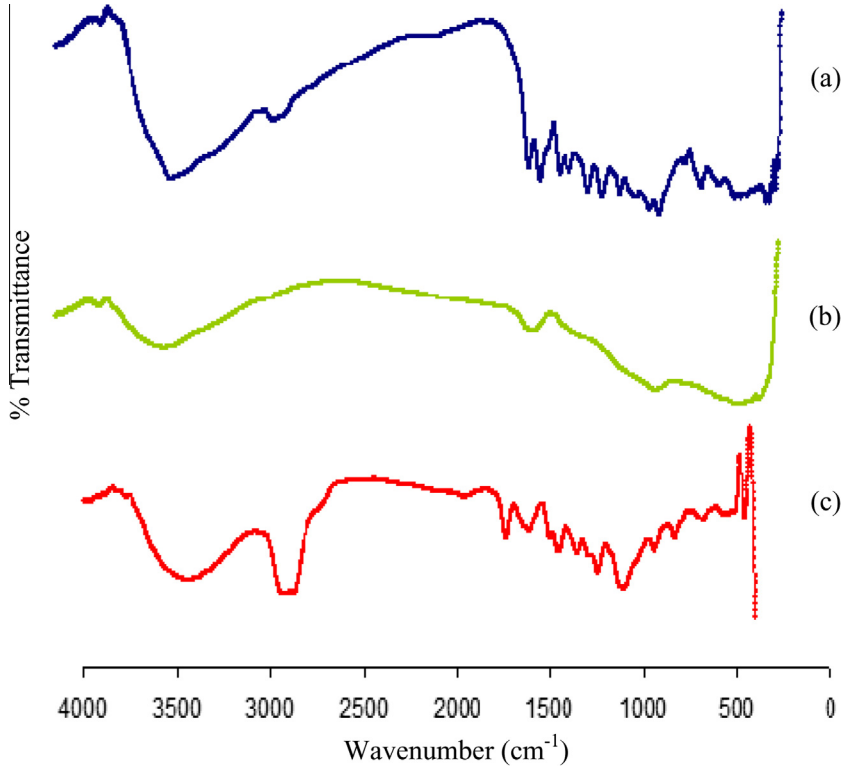

Figure 6 FT-IR spectra of (a) rutin, (b) Neusilin and (c) SS4.

crystals were observed on the surface of the particles. The porous structure and small particle size of the carrier can allow the drug-loaded liquid SEDDS to be entrapped in the core or adsorbed on the surface. Upon contact with an aqueous phase, rapid ingress of the latter into the matrix can be guaranteed, the liquid SEDDS will be rapidly transformed into o/w nanoemulsion, thus making rutin ready for absorption.

3.8.2. X-ray powder diffractometry (XRPD)

The XRPD patterns of rutin, Neusilin and SS4 are shown in Fig. 5. Rutin showed sharp intense peaks, the most characteristic one was recorded at 2-theta value of 26.27° demonstrating the crystalline nature of the drug (Fig. 5a). On the other hand, Neusilin appeared amorphous as it did not show any distinctive peaks over the entire range of the tested temperatures (Fig. 5b). As illustrated in Fig. 5c, the peaks of rutin were completely absent in SS4 indicating the transformation of rutin to the amorphous form in the SSEDDS.

3.8.3. Fourier transform infrared spectroscopy (FT-IR)

Fig. 6 illustrates the FT-IR spectra of rutin, Neusilin and SS4. Pure rutin exhibits an obvious characteristic fingerprint in the region 1500–400 cm^{-1}. Characteristic bands of rutin can be observed at 3424.96 cm^{-1} (OH stretch), 2929.34, 2911.99 cm^{-1} (C-H stretch), 1655.59 cm^{-1} (C═O stretch) and 1600.63 cm^{-1} (aromatic structure) (Fig. 6a). These peaks have appeared in case of SS4 (Fig. 6c) shifted at 3448.1 cm^{-1} (OH stretch), 2927.41 cm^{-1}, 2881.13 cm^{-1} (C-H stretch), 1738.51 cm^{-1} (C═O stretch) and 1617.02 cm^{-1} (aromatic structure). These positional as well as morphological changes in the peaks can prove the physical and/or ionic interaction occurring between the different components and the complete incorporation of the drug within the SEDDS.

4. Conclusion

We can conclude that, in this study, a number of promising self-emulsifying formulations were identified and loaded on recent nano-structured carriers. The SEDDS composed of Triton/Acconon/Labrafac adsorbed on Neusilin® in a 2:1 ratio showed good flow properties and best drug release, proving that delivering the drug in a solubilized and rapidly dispersed manner can be achieved through rational design of lipid-based formulations. The designed liquisolid or solid self-emulsifying powder can provide a promising strategy for the formulation of poorly aqueous soluble lipophilic compounds like rutin.

5. Conflict of interest

None.

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